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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/962,094	10/31/97	BILLING-MEDEL	P 5995.US.P1

EXAMINER	
ART UNIT	PAPER NUMBER
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HM12/0828

ART UNIT 1655

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/962,094	Billings-Medel et al.
Examiner	**Art Unit**
Lisa Athur	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jun 8, 2001

2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 17-29, 31, 32, 34, 36, 37, and 50-69 is/are pending in the applica

4a) Of the above, claim(s) 17-29, 31, 32, 34, 36, and 37 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 50-69 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

1. This action is in response to the paper filed June 8, 2001. Claims 1-16, 30, 33, 35 and 38-49 have been canceled. Claims 50-69 have been newly added. Claims 17-29, 31, 32, 34, 36, 37 are pending but have been withdrawn from prosecution by the previously made restriction requirement. Any rejections made in the previous action which have been reiterated have been obviated by the amendments made to the claims. This action contains new grounds of rejection which have been necessitated by amendment. This action is FINAL.

MAINTAINED REJECTION

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 50-59,69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims have been amended to recite that the method is for detecting the breast cancer by probing with a polynucleotide consisting of SEQ ID NO 1, 2, 3, nucleotides 14-482 of SEQ ID NO 4 or SEQ ID NO 5 and detecting the presence of the target polynucleotide and correlating the presence to the presence of breast cancer. The specification teaches that SEQ ID Nos 1-3 are overlapping EST clones that were identified as being primarily representative of breast tissue

libraries. SEQ ID NO 1-3 were used to make a contig which is SEQ ID NO 4 and SEQ. ID NO 5 represents the consensus sequence. SEQ ID NO 16 is the first forward frame translation of SEQ ID NO 5 which provides a 90 amino acids sequence. SEQ ID NO 4 was compared to the EST database and was found in 85.7 % of breast libraries and only 0.2% of non-breast libraries. The specification teaches that total RNA was obtained from solid breast tissue and from non-breast tissue and used for Northern blot analysis and RT-PCR . Figures 3A and 3B show the results of a Northern blot analysis using SEQ ID NO 1 as a probe with RNA from normal breast tissue, normal prostate and cancer prostrate (3A) and from normal breast tissue and breast cancer tissue (3B). The probe hybridized with all normal breast 1/3 prostate cancer, 0 normal prostate, and 2/6 breast cancer. Table 1 showed than in 2/6 test breast cancer tissues there was over expression of the polynucleotide to which SEQ ID NO 1 hybridized. The evidence in the specification does not predictably teach an association of a polynucleotide to which SEQ ID NO 1 hybridizes with breast cancer because the data is conflictory. In the northern blot analysis only two out of six breast cancer tissue samples showed expression of the polynucleotide complementary to SEQ ID NO 1. Four of the six breast cancer samples did not show expression of the polynucleotide as compared to five out of six normal breast tissue which did express the polynucleotide. From this assay, the skilled artisan would be lead to predict that the absence or decrease in expression of mRNA complementary to SEQ ID NO 1 might by associated with breast cancer as compared to normal breast tissue. However, the data in Table 1 seems to suggest that increased expression of an mRNA complementary to SEQ ID NO 1 was associated with breast cancer. Consequently,

since the teachings in the specification are limited and do not allow the skilled artisan to drawn a reasonable and predictable conclusion as to an association with breast cancer, undue experimentation would be required of the skilled artisan to practice the claimed invention. Furthermore, the specification has not provided any guidance with regard to the presence of absence of a genomic DNA sequence which hybridizes with SEQ ID NO 1-5 and breast cancer. The sequence appears to be present and expressed in normal breast tissue, but no conclusions can be made as to it's presence in the genome of other tissues because no teachings have been provided in the specification.

Response to arguments

The response traverses the rejection on the grounds that a nucleic acid does not require a showing of overexpression in every breast cancer sample to be a useful marker for breast cancer. The response asserts that the HER-2-neu gene is only overexpressed in 1/3 patients and that the estrogen receptor is only expressed in 2/3 patients.

All of the arguments have been thoroughly reviewed but are deemed non-persuasive because the usefulness of the claimed sequences as a breast cancer diagnostic is unpredictable from the evidence given in the specification. The specification has taught that the sequences are present in all breast tissue and overexpressed in only 2 out of 6 tested. A conclusion that this overexpression is indicative of breast cancer can not be drawn because of the low number of samples tested and the very low number of examples of overexpression in breast cancers in light of the expression of this sequence in normal breast tissues. Furthermore, the claims are not drawn

to method of detecting overexpression of the recited sequences but are instead drawn to simply their detection. In specific examples of the Her-2 Neu gene and the estrogen receptor pointed to in the response, very large sample sizes were studied and analyzed for overexpression before a conclusion was drawn that the over expression of these sequence is associated with breast cancer. Therefore, the rejection are maintained

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 50-69 are rejected under 35 U.S.C. 101 because the claimed invention lacks a specific and substantial asserted utility or a well-established utility.

The claims are drawn to a method for detecting breast cancer in a patient by detecting the presence of a polynucleotide consisting of SEQ ID NO 1-4 and correlating the presence of that polynucleotide to breast cancer. This method lacks a patentable utility because there is no specific or substantial use for this method. The specification has not disclosed a correlation between the recited polynucleotide and the existence of breast cancer such that the skilled artisan would be able to have a real world context of use for the claimed method. The specification teaches that SEQ ID Nos 1-3 are overlapping EST clones that were identified as being primarily representative of breast tissue libraries. SEQ ID NO 1-3 were used to make a contig which is SEQ ID NO 4 and SEQ. ID NO 5 represents the consensus sequence. SEQ ID NO 16 is the first forward frame

translation of SEQ ID NO 5 which provides a 90 amino acids sequence. SEQ ID NO 4 was compared to the EST database and was found in 85.7 % of breast libraries and only 0.2% of non-breast libraries. The specification teaches that total RNA was obtained from solid breast tissue and from non-breast tissue and used for Northern blot analysis and RT-PCR . Figures 3A and 3B show the results of a Northern blot analysis using SEQ ID NO 1 as a probe with RNA from normal breast tissue, normal prostate and cancer prostrate (3A) and from normal breast tissue and breast cancer tissue (3B). The probe hybridized with all normal breast 1/3 prostate cancer, 0 normal prostate, and 2/6 breast cancer. Table 1 showed than in 2/6 test breast cancer tissues there was over expression of the polynucleotide to which SEQ ID NO 1 hybridized. The evidence in the specification does not predictably teach an association of a polynucleotide to which SEQ ID NO 1 hybridizes with breast cancer because the data is conflictory. In the northern blot analysis only two out of six breast cancer tissue samples showed expression of the polynucleotide complementary to SEQ ID NO 1. Four of the six breast cancer samples did not show expression of the polynucleotide as compared to five out of six normal breast tissue which did express the polynucleotide. From this assay, the skilled artisan would be lead to predict that the absence or decrease in expression of mRNA complementary to SEQ ID NO 1 might by associated with breast cancer as compared to normal breast tissue. However, the data in Table 1 seems to suggest that increased expression of an mRNA complementary to SEQ ID NO 1 was associated with breast cancer.. The sequence appears to be present and expressed and normal breast tissue, but no conclusions can be made as to it's presence in the genome of other tissues because no

teachings have been provided in the specification. Consequently, this analysis shows that the claimed method has no real world context of use until a correlation can be established between breast disease and the presence of the polynucleotides of SEQ ID NO 1-4. The showing the a particular sequence is over represented in a particular tissue is not considered a specific and substantial utility but is instead considered a general utility which a huge number of polynucleotides all possess.

Response to Arguments

All of the arguments have been thoroughly reviewed but are deemed non-persuasive because the usefulness of the claimed sequences as a breast cancer diagnostic is unpredictable from the evidence given in the specification. The specification has taught that the sequences are present in all breast tissue and overexpressed in only 2 out of 6 tested. A conclusion that this overexpression is indicative of breast cancer can not be drawn because of the low number of samples tested and the very low number of examples of overexpression in breast cancers in light of the expression of this sequence in normal breast tissues. Furthermore, the claims are not drawn to method of detecting overexpression of the recited sequences but are instead drawn to simply their detection. In specific examples of the Her-2 Neu gene and the estrogen receptor pointed to All of the arguments have been thoroughly reviewed but are deemed non-persuasive because the usefulness of the claimed sequences as a breast cancer diagnostic is unpredictable from the evidence given in the specification. The specification has taught that the sequences are present in all breast tissue and overexpressed in only 2 out of 6 tested. A conclusion that this

overexpression is indicative of breast cancer can not be drawn because of the low number of samples tested and the very low number of examples of overexpression in breast cancers in light of the expression of this sequence in normal breast tissues. Furthermore, the claims are not drawn to method of detecting overexpression of the recited sequences but are instead drawn to simply their detection. In specific examples of the Her-2 Neu gene and the estrogen receptor pointed to in the response, very large sample sizes were studied and analyzed for overexpression before a conclusion was drawn that the over expression of these sequence is associated with breast cancer. Therefore, the rejection are maintained.

NEW GROUNDS OF REJECTION

6. Claims 67-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a gene comprising the nucleotide sequence of SEQ ID NO 16. SEQ ID NO 16 is the first forward frame translation, i.e. amino acids sequence, of SEQ ID NO 5 which provides a 90 amino acids sequence. The specification does not support claims to a gene because the specification has provided no description of a genomic sequence. A gene contains exon, ie. coding sequences, and introns, upstream and downstream regulatory regions. None of these elements have been described in this application. The specification also contains no

description of a full length polypeptide which is encoded for the sequence of SEQ ID NO 16. Consequently, these claims are not supported by the instant specification. Because there is no description of the elements which encompass "a gene", Applicant did not appear to be in possession of the claimed invention as the time of filing.

7. Claims 68 and 69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

These claims drawn to "a gene" comprising SEQ ID NO 16 are not enabled by the specification because the specification has provide insufficient guidance to enable the skilled artisan to obtain "a gene" without undue experimentation. The specification has taught several small nucleotide sequences which were obtained from mRNAs expressed in breast tissues. However, the specification has provided no genomic sequences and no information about the location of a gene containing SEQ ID No 16 or SEQ ID Nos 1-5. A gene contains introns, exons and upstream and downstream regulatory regions, none of which have been taught by this application. The structure of "a gene comprising SEQ ID NO 16" (which is an amino acid sequence of only 90 amino acids) is completely unpredictable from the small sequences given in the specification. There is not guidance at all about the remainder of the genomic sequences not

any teachings as to what polypeptide might be encoded by the gene. Consequently, undue experimentation would be required of the skilled artisan to obtain the claimed "gene".

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 67 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite over the recitation of "a nucleic acid sequence selected from the group consisting of SEQ ID NO 16" because SEQ ID NO 16 is not a nucleic acid sequence but is instead an amino acid sequence.

10. No claims are allowable.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa Arthur whose telephone number is (703) 308-3988. The examiner can normally be reached on Monday-Wednesday from 7:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800 1600
August 27, 2001